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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/493,427	01/29/2000	Patrick L. Iverson	0450-0025.30	2225

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/493,427	IVERSON ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12-16-03 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. As a point of clarification, the rejection of claims 28-48 under 35 USC 103(a) as set forth in the Office Action mailed 7-16-03 was over Zalewski et al. in view of Kobayashi et al., Burger et al. Summerton et al., and Agrawal et al. was incomplete. The rejection did not provide a description of the portion of Summerton et al. that was to be applied in the rejection. Therefore, in order to make the record clear a modified rejection is set forth below.

Claim Rejections - 35 USC § 103

4. Claims 28-48 are rejected under 35 USC 103(a) as being unpatentable over Zalewski et al. (US Patent No. 6,159,946) in view of Kobayashi et al., Summerton et al. (US Patent No. 5,378,841), Burger, and Agrawal et al.

Zalewski et al. discloses a method for preventing restenosis in a patient comprising the administration of an antisense oligonucleotide targeting c-myc to the site of injury in a patient, wherein in one embodiment the antisense oligonucleotide comprises 14 contiguous nucleotides of SEQ ID NO: 1 of the instant application (see col. 15-26, example 11). However, Zalewski et

al. does not teach the administration of a c-myc antisense oligonucleotide comprising the full length sequence of the nucleotide sequence as set forth in SEQ ID NO: 1 of the instant application. Additionally, Zalewski et al. does not teach the administration of antisense oligonucleotides in a solution containing at least about 30 mg/ml of the antisense compound, or wherein the derivatized antisense compound comprises a triethyleneglycol moiety, or further wherein the antisense compound is delivered using a biodegradable intravascular stent.

Kobayashi et al. teach the use of antisense oligonucleotides targeting the translation initiation sites of c-myc. These antisense oligonucleotides suppressed the proliferation of MKN-45, a human gastric cancer-derived cell line, and DLD-1, a human colon cancer-derived cell line, in vitro and in vivo. The antisense oligonucleotides comprise phosphorothioate type modifications. The c-myc AO suppressed MKN-45 cell proliferation in vitro at concentration from 0.1-10 mM, and 70% of suppression was obtained with 3-10 mM concentration. The AO decreased the ratio of c-myc positive cells, and the intracellular concentration of c-myc mRNA. Intratumor injection of AO for c-myc (27 mer, AACGTTGAGGGGCATCGTCGCGGGAGG, 10 mM) suppressed the tumor growth of MKN-45 transplanted to the BALB/c mouse. The c-myc antisense oligonucleotide of Kobayashi et al. comprises the nucleotide sequence of SEQ ID NO: 1 of the instant application (abstract).

Summerton et al. (US Patent No. 5,378,841) disclose alpha-morpholino ribonucleoside derivatives and polymers thereof, which are capable of sequence-specific binding to polynucleotides. These alpha-morpholino subunits form stable uncharged linkages and can be used to generate polymers having an uncharged backbone. According to Summerton et al., standard ribo- and deoxyribonucleotide polymers suffer from a number of limitations when used

for base-specific binding to target oligonucleotides. These limitations include (i) restricted passage across biological membranes, (ii) nuclease sensitivity, (iii) target binding which is sensitive to ionic concentration, and (iv) susceptibility to cellular strand separating mechanisms. Furthermore, Summerton et al. state that these limitations can be overcome or minimized by designing polynucleic acid analogs in which the bases are linked along an uncharged backbone (col. 2, lines 10-23).

Burger (WO 98/46740 A1) describes a method of inhibiting restenosis in a patient comprising the administration of an oliogmeric molecule that inhibits the expression of a gene associated with the development of restenosis. The oligomeric compound is preferably a morpholino oligomer compound of morpholino subunit structures, wherein the structures are linked together by uncharged, phosphorous-containing linkages that join the morpholino nitrogen of one subunit to the 5'-exocyclic carbon of an adjacent subunit. Preferably, the phosphorous containing linkages are phosphoramidite linkages (see bridging paragraph of pages 2-3). Additionally, Burger teaches that the oligomeric molecule may be preferably administered to a subject at the site of angioplasty via a perforated or porous catheter balloon, or within a biocompatible polymeric carrier, which may be a hydrogel, e.g. an ethylene oxide/propylene oxide block copolymer. The carrier may also form all or part of an implanted endovascular support device or biodegradable stent (see page 9, lines 1-20).

Agrawal et al. teach modifications which enhance oligonucleotide solubility. In one embodiment Agrawal et al. discloses oligonucleotides comprising a triethyleneglycol moiety (col. 4, lines 8-12).

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant application to modify the method of preventing restenosis in a patient as described by Zalewski et al. with the antisense oligonucleotide of Kobayashi et al. because this antisense oligonucleotide has been disclosed to function successfully in vitro and in vivo to reduce the expression of c-myc. Furthermore, one of skill in the art would have been motivated to use the antisense oligonucleotides of Kobayashi et al. because it would have been obvious to replace one functionally equivalent antisense oligonucleotide targeting c-myc with another.

It would have been obvious to one of ordinary skill in the art at the time of filing to modify the method of Zalewski et al. to comprise the administration of antisense oligonucleotides comprising internucleoside linkages having morpholino modifications as taught by Summerton et al. and Burger, and to comprise the use of a biodegradable stent as taught by Burger. One of ordinary skill in the art would have been motivated to use morpholino modified oligomers of Summerton et al. or Burger, because Burger clearly teach the reduction of restenosis in an animal comprising the administration of morpholino modified oligomers via a biodegradable stent.

Moreover, it would have been obvious to one of ordinary skill in the art to modify the oligonucleotides of Zalewski et al. with triethyleneglycol modifications as described by Agrawal, since these modifications enhance the solubility of the antisense oligonucleotides. Furthermore, one of ordinary skill in the art would have been motivated to use antisense oligonucleotides having enhanced solubility as modified by the method of Agrawal et al. since these antisense oligonucleotides are to be used in an aqueous biological environment. Agrawal et al. also teach that these moieties can be used to form oligonucleotide multimers, such multimers would

enhance the effective concentration of the oligonucleotide and therefore increase the efficacy of an antisense compound. Burger also describe the use of polyethylene oxide block copolymers as a drug delivery device, see page 9, lines 7-9, therefore triethyleneglycol modifications would have been expected to enhance the delivery of antisense compounds into cells.

Applicant's method recites the use of an antisense compound in an amount of about 0.5 to 2 mg or in a solution containing at least about 30 mg/ml. Zalewski et al. teach the use of antisense oligonucleotides in their disclosed methods in amount of between about 1 to 100 μM and more preferably between 1 to 10 μM. Although the method of Zalewski et al. does not recite the exact amount of antisense compound as recited in Applicant's method, absent evidence to the contrary it would have been obvious to one of ordinary skill in the art to optimize the conditions of an experiment or reaction in order to maximize the desired results.

Therefore, the invention as a whole is *prima facie* obvious Zalewski et al. (US Patent 6,159,946) in view of Kobayashi et al., Summerton et al., Burger, and Agrawal et al.

Response to Arguments

5. It is noted that although the rejection of claims 28-48 under 35 USC 103(a) as set forth in the Office Action mailed 7-16-03 was incomplete, to the extent that it did not include a description of the Summerton et al. reference, Applicants responded to the rejection based upon their interpretation as how the examiner would have interpreted the Summerton et al. reference.

6. Claims 28-48 remain rejected under 35 USC 103(a) as being unpatentable over Zalewski et al. (US Patent No. 6,159,946) in view of Kobayashi et al., Summerton et al. (US Patent No. 5,378,841), Burger, and Agrawal et al., for the reasons of record set forth in the Official Action mailed 7-16-03 and for those reasons set forth above.

7. Applicant's arguments filed 12-16-03 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the combination of Zalewski et al., which shows the effect of a phosphorothioate-linked anti-c-myc oligonucleotide in an animal model of restenosis, and Burger et al., which teaches the use of an anti-CMV morpholino oligomer, without supporting data, would not provide a reasonable expectation that the presently claimed oligomers would effectively inhibit restenosis at a vascular injury site in a patient, as demonstrated by the data previously presented in the Weller Declaration submitted on May 1, 2002.

The examiner recognizes the unexpected results demonstrated with the administration of the phosphorodiamidate morpholino antisense compound comprising the sequence according to SEQ ID NO: 1 of the instant application, for treatment of restenosis in a human patient as set forth in the Weller Declaration. Applicant's results suggest that the prior art did not appreciate the benefits of the combination of phosphorodiamidate and morpholino modifications in a known antisense compound targeting c-myc (see Kobayashi et al.) for the treatment of restenosis in a human patient. Unexpected results are therefore acknowledged for applicant's methods of treatment comprising the administration of phosphorodiamidate morpholino antisense compounds comprising the sequence according to SEQ ID NO: 1 in a human patient.

However, it is noted that the instant claims are not limited to the treatment of a human patient, nor are they limited to the administration of a phosphorodiamidate morpholino antisense compound comprising the sequence according to SEQ ID NO: 1 of the instant application. Although Applicants emphasize that a "patient" is distinct from an animal model; see, for example, the specification at page 15, lines 10-11 ("administered to a patient or in an animal

model"; emphasis added), Applicant's argument that the term "patient" as recited in the claims does not encompass an animal is not convincing. Applicant's definition can be interpreted as suggesting that the animal model and the patient are equivalent systems, i.e. that results achieved using an animal model would be predictive of results expected in a patient. Therefore, since it is the examiner's position that the term "patient" as recited in the instant claims may encompass an animal, Applicant's arguments that the Zalewski et al. patent is not enabling in any patient, including an animal "patient" are not persuasive, because Zalewski et al. had previously demonstrated that a modified antisense compound targeting c-myc would function to inhibit restenosis in an animal. Applicants have not provided sufficient evidence that the antisense compounds disclosed by Zalewski et al. and modified according to Kobayashi et al., Summerton et al., Burger and Agrawal et al. would not function to inhibit restenosis at a vascular injury site in a patient, wherein said patient is an animal.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Epps-Ford, Ph.D.
Patent Examiner
Art Unit 1635

JLE